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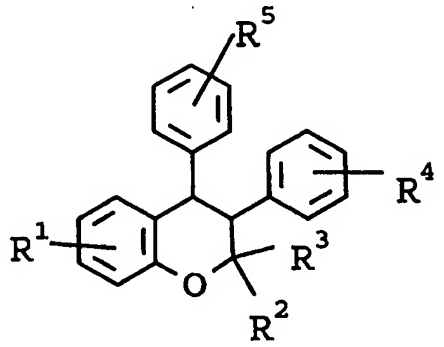
Published
With international search report.

(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR INCREASING LIBIDO IN POST-MENOPAUSAL WOMEN

(57) Abstract

The present invention provides novel uses of compounds of general formula (I) wherein R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino) (C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for increasing libido in post-menopausal women.



(I)

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AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for increasing libido in post-menopausal women

FIELD OF THIS INVENTION

The present invention relates to the use of compounds of the general formula I for increasing libido in post-menopausal women. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THIS INVENTION

The medical advances made in the second half of this century have resulted in increases in both the length and the quality of life. One result of this trend is a rapidly ageing population and an increasing demand for new therapies to treat the problems which result from the ageing process.

One such problem is that of sexuality in peri- and post-menopausal women. While there is a decline in libido with age in women, an accelerated reduction occurs with the menopause. Several studies have shown that between one third and one half of menopausal women complain of a problem in one or more aspects of sexual functioning. Kinsey,A,C., et al (Sexual Behaviour in the Human Female, Saunders;PA, 1953) showed a 53% reduction in frequency of coitus in menopausal women, whilst a longitudinal study of women in Sweden found a 52% decrease in sexual interest and a 20% decrease in orgasm (Hallstrom,T, Sexuality in the climacteric. Clin Obstet Gynecol 1977;4:227-239). This study established statistically that these decrements in sexual functioning were related to the menopause and not ageing per se. Other survey studies of menopausal women have confirmed decreases in sexual interest of 33% (Hallstrom,T, Samuelsson,S, Changes in women's sexual desire in middle life : the longitudinal study of women in Gothenburg. Arch Sex Behav 1990;19:259-268), 85% (McCoy,N.L., Davidson,J.M., A longitudinal study of the effects of menopause

on sexuality .Maturitas 1985;7:203-210) and 39% (Sarrel,P.M., Whitehead,M.I., Maturitas;7:217-224). Pfeiffer, E., Etal (Terminus of sexual behaviour in middle and old age , Journal of the American geriatric society 1972;pg 2151-2158) showed the most dramatic change in sexuality took place postmenopausaly between the ages of 50 - 60years. A recent study (Davis,S:R., Etal Testosterone enhances estradiol's effects on postmenopausal bone density Maturitas 1995;21: pg 227-236) documented both the loss of sexuality in post-menopausal women and the beneficial effects of estradiol.

While there is no proven direct link between declining oestrogen levels and declining sexual function, it may be hypothesised that as sex hormone levels fall following natural and surgical menopause this fall may contribute to the negative changes in sexuality in this population of women.

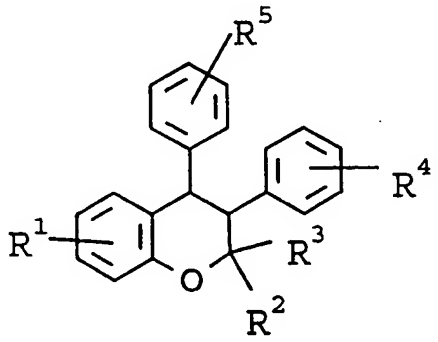
Centchroman is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent Specification No. 4,447,622; Singh et al., Acta Endocrinal (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

U.S. patent 5,453,442 describes methods of lowering serum cholesterol and inhibiting smoother muscle cell proliferation in humans and inhibiting uterine fibroid disease and endometriosis in women by administering compounds of formula I as shown therein. Furthermore, US patent 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diaryl chromans and their pharmaceutically acceptable salts. There is no disclosure in the patents of using the compounds to increase libido in post-menopausal women.

There remains a need in the art for compositions and methods useful for increasing libido in post-menopausal women.

DETAILED DESCRIPTION OF THIS INVENTION

This invention provides the use of a compound having the formula



(I)

wherein R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for increasing libido in post-menopausal women.

The current invention concerns the discovery that the compounds of formula I are useful for increasing libido. The methods of treatment provided by this invention are practiced by administering to a human in need a dose of a compound of formula I or a pharmaceutically acceptable salt thereof, that is effective to increase libido.

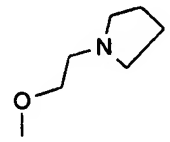
The term "post-menopausal women" is defined to include not only women of advanced age who have passed through menopause, but also women who have been oophorectomised, hysterectomized or oophorohysterectomised or for some other reason have suppressed estrogen production, such as those who have un-

dergone long-term administration of corticosteroids, suffer from Cushions' syndromes or have gonadal dysgenesis.

The expression "libido" as used herein refers to those aspects of the human psyche which are related to sexual interest and drive. Additionally, the expression "libido" refers to related psychic attitudes concerned with mental well-being and which refer to such characteristics as mental alertness and activity, creativity, enthusiasm, sociability and an awareness of interpersonal relationships. Libido is generally recognized to be the result of a complex interaction of factors in which genetic, anatomic, neurologic, psychologic and biochemical factors all play prominent roles. The exact mechanism by which the compounds of the present invention achieve this effect is not understood except to the extent that it is attributable to a biochemical mechanism.

Within formula I, R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or a C_{1-6} alkyl. As used herein, the term "C_{1-6} alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term "C_{1-6} alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amyloxy, sec-amyloxy, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. Herein, the term "(tertiary amino)(C_{1-6} alkoxy)" is a C_{1-6} alkoxy group which is substituted by a tertiary amino radical. The tertiary amino radical may be a N,N-dialkylamine such as a N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino or a polymethyleneimine, e.g., piperidine, pyrrolidine, N-methylpiperazine or morpholine. Preferred compounds include those in which R^1 is C_{1-6} alkoxy; R^2 and R^3 are C_{1-6} alkyl, especially methyl; R^4 is hydrogen; and R

^{5} is (tertiary amino)(C_{1-6} alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R^1 is in the 7-position and is C_{1-6} alkoxy, particularly methoxy; each of R^2 and R^3 is methyl, R^4 is hydrogen, and R^5 is in the 4-position and is a (tertiary amino)(C_{1-6} alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy with formula II

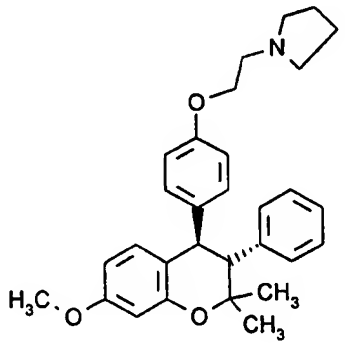


(II)

To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated d- or l- enantiomers may be used. The trans-l-enantiomers are more preferred.

A particularly preferred compound for use within the present invention is centchroman having the formula IV



(IV)

Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l- nantiomers, as well as the racemic mixture, are included.

3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney et al., U.S. Patent Specification No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. If R^2 is different from R^3 and R^4 is different from R^5, the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, maleic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. A preferable salt is the hydrogen fumarate salt.

3,4-diarylchromans of formula I and their salts are useful within human medicine in the treatment of patients suffering from a decline in libido. For use within the present invention, 3,4-diarylchromans of formula I and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or

transdermal administration according to conventional methods. Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds of formula I in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

Oral administration is preferred. Thus, the active compound of formula I is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound of formula I is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount required to increase libido, according to this invention. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art. A typical daily dose will contain a nontoxic dosage range of from about 0.001 to about 75 mg/kg patient per day of a compound of the present invention.

The pharmaceutical compositions containing a compound of formula I may be administered in unit dosage form one or more times per day or week. In the alternative, they may be provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Con-

trolled-release formulations are disclosed by, for example, Sanders et al., J Pharm Sci 73 (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

Examples of preferred compounds of formula I are centchroman as a racemic mixture and as isolated l-centchroman and d-centchroman enantiomers. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound. The more preferred compound is isolated l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, succinic acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLES

Test 1

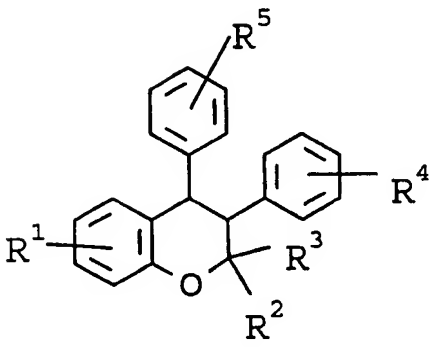
The animals used are ovariectomized Sprague Dawley rats (Møllegaard Denmark) weighing 250-300 grams Food and water are available ad libitum. A compound

of the invention (or oestrogen) is administered to one group of rats, and the other group is maintained as a control. Behavioural observations are made by placing each female with a cage adapted, sexually experienced male and measuring the number of females exhibiting lordosis (dorsi-flexion of the spine). In each female exhibiting lordosis the lordosis quotient (L.Q. = ratio of the number of lordoses to the number of mounts x 100) was calculated. Only the females being mounted at least once by the male were included in the L.Q. calculations. Tests were concluded when the females had received 10 mounts or after 15 min whichever came first. The tests were carried out in subdued lighting.

Activity is shown as a positive effect on either of the above measures.

CLAIMS

1. The use of compounds of the general formula I



(I)

wherein R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof , for the manufacture of a pharmaceutical composition for increasing libido in post-menopausal women.

2. The use, according to claim 1, wherein R^1 in the compound used is C_{1-6} alkoxy, R^2 and R^3 are C_{1-6} alkyl, R^4 is hydrogen and R^5 is (tertiary amino) C_{1-6} alkoxy.

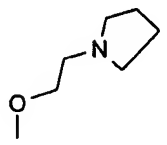
3. The use according to any one of claims 1 or 2 wherein R^1 is methoxy.

4. The use according to any one of claims 1-3 wherein R^2 is methyl.

5. The use according to any one of claims 1-4 wherein R^3 is methyl.

6. The use according to any one of claims 1-5 wherein R^4 is hydrogen.

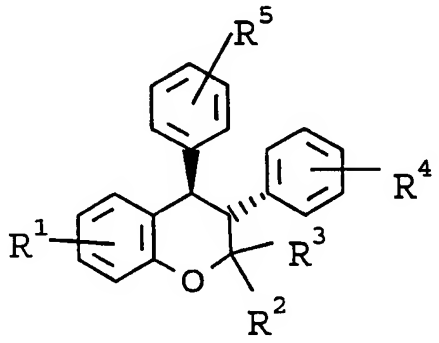
7. The use according to any one of claims 1-6 wherein R^5 is a group as stated in formula II below:



(II)

8. The use according to any one of claims 1-7 wherein said compound is an isolated d- or l-enantiomer.

9. The use according to any one of the preceding claims wherein said compound has the general formula III as stated below:



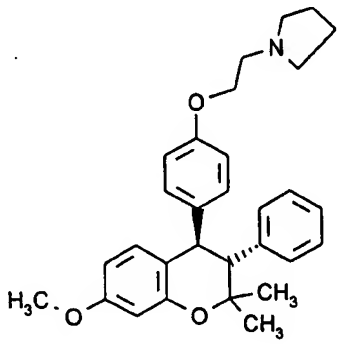
(III)

wherein R^1, R^2, R^3, R^4 and R^5 each are as defined in above claim 1.

10. The use according to anyone of the preceding claims wherein said compound is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman.

11. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

12. The use according to claim 1 wherein said compound is centchroman 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman having the formula IV as stated below:



(IV)

13. The use according to claim 12 wherein said compound is an isolated l-enantiomer of 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman.

14. The use according to any one of the preceding claims wherein said composition is in a form suitable for oral administration.

15. The use according to any one of the preceding claims wherein said compound is administered as a dose in a range from about 0.001 to 75 mg/kg patient per day.

16. The use according to any one of the preceding claims wherein said composition is administered one or more times per day or week.

17. The use according to any one of the preceding claims wherein said composition is in the form of a dermal implant.

18. Method for increasing libido in post-menopausal women comprising administering to a patient a clinically effective amount of a compound of above

formula I stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to increase libido in post-menopausal women.

19. A method of increasing libido in post-menopausal women which method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00031

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0178862 A2 (BCM TECHNOLOGIES, INC.), 23 April 1986 (23.04.86) -- --------	1-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1998	13-05-1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18, 19
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/04/98

International application No.
PCT/DK 98/00031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0178862 A2	23/04/86	SE 0178862 T3	
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